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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	9

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DATE MAILED: 10/02/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 9/18/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 53, 55, 57, 65-67, 71 + 74-98 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 53, 55, 57, 65-67, 71 + 74-98 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 6 & 9/12/99 + 10/8/99
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

The preliminary amendment of 10/21/99 has been entered. The amendment canceled claims 3, 5, 6, 10, 11, 13, 16-19, 23-25, 27-29, 31, 34, 36-40, 42, 50-52, 54, 56, 58-64, 68-70, 72 and 73, and amended claims 14, 22, 26, 30, 33, 35, 41, 49 and 71.

After the above amendment, claims in the application were 1, 2, 4, 7-9, 12, 14, 15, 20-22, 26, 30, 32, 33, 35, 41, 43-49, 53, 55, 57, 65-67 and 71.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2, 4, 7-9, 12, 14, 15, 20-22, 26, 30, 32, 33, 35, 41 and 46-49, drawn to a method of attaching an agent to body tissue, classified in class 424, subclass 520

II. Claims 43-45, drawn to a method of sealing tissue, classified in class 424, subclass 400.

III. Claims 53, 55, 57, 65-67 and 71, drawn to a composition containing a conjugate of an agent and a linking molecule, classified in class 435, subclass 174.

The inventions are distinct, each from the other because:

The invention of each group can be performed without the invention of any other group. The conjugate of the composition of Group III can have uses other than for bonding an agent to tissue as in Group I or sealing tissue as in Group II. The composition can be used for bonding an agent to a non-tissue material such as a polymer unrelated to tissue, and where there is no sealing of tissue. The sealing of tissue in Group II does not requiring bonding an agent to tissue as in Group I.

Conversely, the bonding of an agent to tissue in Group I does not require sealing of tissue as in Group II.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Edward R. Gates on 9/13/00 a provisional election was made without traverse to prosecute the invention of Group III, claims 53, 55, 57, 65-67 and 71. Claims 1, 2, 4, 7-9, 12, 14, 15, 20-22, 26, 30, 32, 33, 35, 41 and 43-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

In a response of 9/18/00 following the restriction requirement, applicants canceled the non-elected claims, and added claims 74-98 that are the same (renumbered) as claims previously canceled by a preliminary amendment of 10/21/99 that were dependent on the elected claims in Group III.

Claims examined on the merits are 53, 55, 57, 65-67, 71 and 74-98 which are all claims in the application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 86, 89, 92, 95 and 98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to enable a kit as claimed containing a third container containing a linking molecule that is a substrate of transglutaminase and that is covalently attached to the composition contained in the first container if in the presence of transglutaminase. No enabling description of this embodiment is found. While examples 1 and 2 describe a three vial or three component kit, the first is the composition containing the agent and linking molecule, the second is a calcium chloride activator and the third is a transglutaminase preparation. No description is found of a third container containing a linking molecule as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53, 55, 57, 65-67, 71 and 74-98 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 53 and where required in other claims, "linking molecule having a carboxamide, the linking molecule being a carboxamide-bearing substrate of transglutaminase" is confusing and unclear. The relationship between the carboxamide and the carboxamide-bearing substrate is unclear. If the linking molecule is a carboxamide-bearing substrate, then what is the purpose of requiring the linking molecule to have a carboxamide. It is presumed that "carboxamide-bearing substrate" means a substrate containing a carboxamide.

Claim 55 is confusing by being dependent on canceled claim 54.

The claims are confusing and unclear by "nonextracellular matrix" and "nonlabeling agent" in line 2 of claims 53 and 65 being uncertain as to meaning and scope. Materials that are not an extracellular matrix and a labeling agent within the Markush group of agents in the claims is relative and subjective.

In claim 65 (bridging lines 2 and 3), "polymer having multiple units carrying a polyaliphatic amine" is uncertain as to meaning and scope. It is uncertain as to the part of the polymer that is a unit. A polymer by its intrinsic nature contains multiple units of monomers used to form the polymer. Is this what is required? If the units are the monomers, multiple units should not be required since a polymer inherently contains multiple units or otherwise it is not a polymer. The meaning of "carrying a polyaliphatic amine" is uncertain. Does the polyaliphatic

amine form the unit or is the amine in addition to the unit and attached to the unit.

In line 9, claim 65 is unclear as to the relationship of the "at least 3 aliphatic amines" to the units and polyaliphatic amine required in line 2.

Bridging lines 1 and 2 of claim 76, "polymer rich in glutamine" is uncertain as to meaning and scope. An amount that is "rich" is relative and subjective.

Claim 77 is unclear as to how claim 53 is further limited. The Markush group of agents in claim 77 appears to contain the same members as the Markush group of agents in claim 53, except that claim 77 requires a ligand and a receptor (lines 4 and 5) as separate members that are not in the Markush group of claim 53. A dependent claim cannot add members to a Markush group previously claimed. A dependent claim can only further limit a Markush group previously claimed by reducing the number of members in the group or by further limiting a specific member.

Claim 82 is confusing by requiring the agent when in native form and free of conjugation to the linking molecule not to be a substrate for transglutaminase. If the agent in native and free form is not a substrate, then the native agent when conjugated to the linking molecule will also not be a substrate. Claim 82 should merely require the agent not to be a substrate for the transglutaminase.

In claims 86, 89, 92, 95 and 98, the meaning and scope is uncertain of "third container containing a linking molecule that is a substrate of transglutaminase and that is covalently attached to the composition contained in the first container if in the presence of transglutaminase"

The specification does not describe a third container containing this linking molecule. Since the composition in the first container is a conjugate of an agent and a linking molecule, the purpose of a linking molecule in a third container is uncertain. Additionally, how can the linking molecule in the third container covalently attach to the conjugate in the first container? Also, the meaning of covalent attachment being only in the presence of transglutaminase is uncertain. Does the transglutaminase cause covalent attachment of the linking molecule to the composition?

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53, 55, 57, 65-67, 71 and 74-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al (5,490,980) in

view of Kahlem et al (CD), Greenberg et al (CF) and Davies et al (CA), and if necessary in further vies of Green et al (5,525,336).

Claim 53 and claims dependent thereon are drawn to a conjugate of a nonextracellular matrix, nonlabeling agent and a linking molecule that is a carboxamide-containing substrate of transglutaminase. Claim 65 and claims dependent thereon require a conjugate of the agent and a polymer having multiple units carrying a polyaliphatic amine that is a substrate of transglutaminase. Also claimed are kits having a first container containing the conjugate of claim 53 or 65 and a second container containing transglutaminase.

Richardson et al disclose (col 2, lines 44-58) a composition containing an active ingredient modified to contain an $-RNH_2$ moiety where R is a straight aliphatic hydrocarbon chain of 1 to 8 carbon atoms and preferably at least 5 carbon atoms. Transglutaminase uses the $-RNH_2$ moiety as a substrate to bind the active ingredient through the $-RNH_2$ moiety to glutamine residues in skin, hair or nails. Most preferably the active ingredient contains more than one $-RNH_2$ moiety in order to obtain enhanced binding of the active ingredient.

Kahlem et al, Greenberg et al and Davies et al disclose transglutaminase crosslinking by acting on carboxamide-containing substrates.

Green et al disclose transglutaminase crosslinking proteins together by forming bonds between glutaminyl and lysyl residues.

It would have been obvious to link the active agent of Richardson et al to a carboxamide-containing substrate of transglutaminase since it would have been expected from Kahlem et al, Greenberg et al and Davies et

al that this substrate will substitute for the function of the $-RNH_2-$ containing moiety of the active agent of Richardson et al by the transglutaminase catalyzing a reaction between a carboxamide of peptide-bound glutamine and a primary amino group (RNH_2) of peptide-bound lysine. As to claim 65, the $-RNH_2$ moiety of Richardson et al is an aliphatic amine. To provide a polymer such as a lysine-containing protein or peptide having the $-RNH_2$ moiety for attaching the active ingredient of Richardson et al would have been a matter of obvious choice since it would have been apparent from Kahlem et al, Greenberg et al and Davies et al that the carboxamide group and the primary amino group of RNH_2 can both be contained by a peptide or protein, and that crosslinking or attachment will occur irrespective of which protein or peptide contains the active ingredient. Forming a kit as required in claims 71 and 86-98 would have been obvious to provide the active ingredient of Richardson et al in a form ready to use for bonding to skin, hair or nails. Having transglutaminase in a separate container would have been obvious to prevent its acting on the substrate before crosslinking is desired. If needed, Green et al would have further suggested that different substrates for transglutaminase can be used.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1651